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NEUTRON THERAPY AND SPECIFIC IONIZATION

JANEWAY MEMORIAL LECTURE*

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MR. PRESIDENT, members and guests of the American Radium Society, I want to thank the Society for the honor of being selected to deliver the 1947 Janeway Lecture. It is a great privilege to be allowed to participate in this means of remembering Dr. Janeway. I never had the pleasure of knowing Dr. Janeway personally, but his work and the contributions he he made to our specialty, both directly and through those whom he inspired, are known to all of us. Were he here today, he would be keenly interested in the results of a type of radiation therapy that was not known in his active days.

Neutrons were identified in 1932. Intensive treatment of human cancer with them was started in 1938 and continued until early in 1943. More than four years have passed since the last treatment was given. I hope, by a review of the results of those treatments and of animal experiments, to show that:

1. The theoretical reasons for testing the biological effects of neutrons were sound;
2. The practical reasons for an early trial of the effects on human cancer, while appearing sound, did not envisage the late effects;
3. The late effects from the irradiation of animals with neutrons are greater in proportion to the early effects than would be expected from previous experience with such effects from irradiation with roentgen rays;
4. The rate of administration of any radiation plays a bigger role than most of us have believed probable; in other words, the distribution of ions in "time" as well as in "space" is significant;
5. Neutron therapy as administered by us has resulted in such bad late sequelae in proportion to the few good results that it should not be continued;
6. The late results from the use of neutrons should serve as a warning to those proposing to use protons, multimillion volt beta rays and multimillion volt roentgen rays in the treatment of human cancer.

NEUTRONS AND FAST NEUTRON BEAMS

Neutrons, as you all now know, are particles of matter of the same weight as the

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nuclei of hydrogen atoms. They have no electrical charge. They do not ordinarily exist free in nature, but are part of the nucleus of all atoms except those of hydrogen. They may be obtained by knocking them out of atomic nuclei by bombardment with high energy photons or atomic particles. The method used at the University of California to obtain a beam of fast neutrons has been described on several occasions.[1] The cyclotron devised by E. O. Lawrence was used to give multimillion volt energy to deuterons which struck a beryllium target. From this target neutrons came forth with great energies. Aebersold[2] developed a collimating device such that clean-cut beams of varying sizes could be obtained.

Because of the structure of the cyclotron the beam of neutrons came out horizontally. This type of beam is very difficult to use as any of you know who have had experience with fixed horizontal beams. When patients have to lie on their sides for long treatments they tend to slip out of position. Moreover, the contents of the body cavities assume unusual positions when patients are placed on their sides. This handicap contributed some share to our bad results. The physical arrangement for treatments has been described in previous publications dealing with the early effects.[1,12,13]

MEASUREMENT OF NEUTRON RADIATION

Among the first problems to be solved was how to measure neutrons so as to be able to reproduce exposures and to compare results with those from other types of radiations. An "absolute" unit of measurement, such as the roentgen, was not, and still is not, available. However, since ionization results secondarily from the absorption of energy from neutrons, the same thimble chambers as are used to measure roentgen rays can be used, but the readings do not have the same significance. We used the 100 r chamber of the Victoreen condenser r-meter as made in 1938, but we called the units on the scale n units instead of roentgens. This provided a means of reproducing exposures. Aebersold and Anslow[3] determined experimentally that the energy absorbed in tissue was approximately the same from a free air exposure of 1 n as from one of 2.5 r, the neutrons being generated by 16 mev and the roentgen rays by 220 kv. Parker has suggested the use of the term rep (roentgen equivalent physical) to express tissue doses for radiations that cannot be measured in roentgens. One rep means that the energy absorbed per gram of tissue is the same as that from an exposure of 1 roentgen. On this basis, 1 n = 2.5 rep. The advantage of this unit lies in the fact that biological effects can be compared on the basis of similar energy absorption from various radiations rather than on the basis of arbitrary units. In most of the early literature and many recent publications, the neutron and roentgen-ray exposures required to produce the same biological effect are compared by the r/n ratio. Since it usually requires more roentgens of roentgen rays than n units of neutrons, neutrons are said to be more efficient. This is somewhat like saying that because it takes 12 inches of an inch rule and 1 foot of a foot rule to reach between two points, the foot rule is more efficient. The units must be physically equivalent if proper comparisons are to be made. Whenever doses of neutrons are specified in n units, they can be multiplied by 2.5 to bring them to reps and thereby placed on a basis of equal energy absorption per unit for better comparison with doses of roentgen rays expressed in roentgens.

Gray,[6] after using several methods of measuring neutron radiation, decided to express exposures in "energy units." He defines his unit of dose as "that amount of neutron radiation which produces an increment of energy in unit volume of tissue equal to the increment of energy produced in unit volume of water by one roentgen of gamma radiation." His unit is essentially the same as Parker's rep.

RELATIVE BIOLOGICAL EFFECTIVENESS

Before any treatments of cancer patients were initiated, a considerable amount of biological experimentation was completed

and a lot more has been accomplished since. In almost all of the investigations reported using a wide variety of cells and organisms it has been found that the *qualitative* effects of different radiations are indistinguishable from each other. Two exceptions should be noted. Spear and Tansley[11] found that neutrons cause more primary cell degeneration—as distinct from degeneration at the time of mitosis—than gamma rays, and Marshak[9,10] came to the conclusion that neutrons had more effect than roentgen rays on cells in the "resting" stage, both of these being qualitative changes. On the other hand, the *quantitative* effects—the effects produced by physically equivalent exposures—of various radiations have differed significantly.

The relative biological effectiveness of neutrons to roentgen rays can be expressed as the ratio of the number of roentgens of roentgen rays to the number of reps of neutrons required to produce the same biological effect. When this ratio is 1 the biological effect is produced by the absorption of the same amount of energy from both radiations. When it is greater than 1, the biological effect under consideration is caused by the absorption of less energy from the neutron beam than from the roentgen-ray beam; in other words, the neutron radiations are more effective per unit of energy absorbed. Applying this basis to the published results of various investigators it is found that the relative biological effectiveness varies greatly from one test object to another. Lewis[8] found that the relative biological effectiveness for the inhibition of growth of chick embryo fibroblasts in tissue culture was 0.8, i.e. neutrons were less effective than roentgen rays. Zirkle and Lampe[15] found that the relative biological effectiveness for the inhibition by 50 per cent of hatching of *Drosophila* eggs varies from 0.76 for $1\frac{1}{2}$ hr. eggs to 1.24 for $4\frac{1}{2}$ hr. eggs, i.e. neutrons were less effective in the first case and more effective in the second case than roentgen rays. Axelrod *et al.*[4] found the relative biological effectiveness for the inhibition of growth of a mouse lymphosarcoma irradiated in vitro to be 3. Gray *et al.*[5] have recently reported the relative biological effectiveness for regression of mouse tumors irradiated in vivo to be 20, but they used neutrons with lower energies than most American investigators have used.

It was thus obvious quite early, and has become more so recently, that the biological effectiveness of neutrons relative to roentgen rays varied from one tissue to another. The great question in regard to the treatment of human cancer was, would the effect on cancer cells relative to that on normal cells be greater for neutron than for roentgen-ray radiations? In 1938 we felt that no amount of animal experimentation would answer this question. In the tumor service of the University of California Hospital Out-Patient Department there were, as in all clinics, a number of patients with incurable cancer. It was felt that the prospect of helping these patients was sufficiently great to justify trying the effects of irradiation with neutrons. The early results of those treatments have been published[12,13] and here only a few pertinent facts will be reviewed.

It was found that a threshold skin reaction closely paralleling that from roentgen rays could be produced on the forearm with an r/n ratio of 7 for 8 mev neutrons and 6 for 16 mev neutrons, i.e. the relative biological effectiveness was 2.8 and 2.4 respectively. The relative biological effectiveness for a first degree erythema of face from a single dose was 2 (r/n = 5/1). But we found also that increasing the dose of neutrons required to produce the first degree erythema by 50 per cent did not cause an epidermolysis, whereas we would have expected that reaction from such an increase of dose of roentgen rays. Hence, at that time we should have been warned that the ratio of doses required was not the same for all effects on the skin. In other words, the relative biological effectiveness of neutrons to roentgen rays was somewhat less for the more severe reaction. It will be shown by results reported later in this lecture that the relative biological effectiveness of neutrons as judged by late skin and

subcutaneous reactions is much larger. Thus, even on human skin and subcutaneous tissue one cannot extrapolate the relative biological effectiveness from one reaction to another.

SPECIFIC IONIZATION AND BIOLOGICAL EFFECT

The reason for these variations in biological effectiveness is not known and no satisfactory theory has yet been propounded. While many facts are known, the correlation of them is not clear. Because the biological effects from roentgen rays of any given quality are proportional to the ionization in the tissues, it might be assumed that the effects are the direct result of the ionization. Since the amount of energy absorbed is proportional to number of ion pairs formed, it might be assumed further that a given biological effect would be produced by the absorption of a specific amount of energy per gram of tissue. However, every radiologist knows that more tissue roentgens are required to produce a given reaction when gamma rays are used than when roentgen rays generated by 200 kv. are used; yet a tissue roentgen of either one is supposed to represent the same number of ion pairs per gram and the same number of ergs absorbed per gram. When neutrons are considered still greater biological differences result from the formation of the same number of ion pairs or the absorption of the same number of ergs per gram.

Photons transfer their energy to electrons and these in turn cause the ionization. The number of ions produced along the path of an electron varies inversely with the velocity (energy) of the electron. High energy roentgen rays produce more high energy electrons and hence a greater distance between the ions produced. The number of ion pairs produced per unit length of the ionization tracks is called the specific ionization. It is therefore an inverse measure of the spacing of the individual ion pairs along the tracks of the ionizing particle.

Neutrons transfer their energy in tissue mainly to protons and these in turn cause ionization. Since the proton has a much greater mass than the electron, its velocity is much less than an electron having the same energy, and therefore the density of ions along its path is much greater, but the path is shorter. From these facts, it is obvious that even when the total ionization in a gram of tissue is the same from roentgen-ray and neutron radiations the spatial distribution of the ions within the gram will be different. Many tissue cells or protein molecules will be penetrated by the electrons, but few of them will have more than one or two ion pairs produced in them, whereas only a few will be penetrated by the protons, but those few will have many ions produced within them. If only one or two ions per cell are required to produce a given effect roentgen rays should be more effective, but if many ions are required, neutrons should be more effective. After a comprehensive review of the literature, Zirkle[14] concluded that in producing most types of acute injury to the higher plants and animals a radiation is likely to be more effective the greater the number of ion pairs produced per unit length of the track of the ionizing particles. Stated in another way, the greater the specific ionization, the greater the biological effectiveness on higher animals.

It must be remembered that the process of ionization accounts for only about one-half of the energy transferred from the radiation to the tissues. One of the other processes that occurs is the excitation of molecules which may result in the breaking of chemical bonds. Too little is known about the role that this plays in producing biological effects. It may well be that such energy transfer does not always run parallel to ionization and hence to measurements in roentgens or reps. There are other chemical changes induced by irradiation such as the initiation of the chain reaction of the combination of many hydrogen ions with chlorine resulting from the initial ionization of only one hydrogen molecule in the presence of chlorine. I am incapable of discussing these phenomena further. They are

mentioned because I did not want to leave you with the impression that we must study only the spatial distribution of ions in an attempt to explain the difference in effectiveness of various radiations on biological materials.

PILE NEUTRONS

With the advent of the self supporting chain reacting nuclear fission piles, interest in the effects of radiations, and especially of neutron rays on biological material, extended far beyond the circle of therapeutic radiologists. The safety of thousands of workers became involved. The energy of the neutrons from fission is much less than that of most of those produced on cyclotrons. Gray and others had shown that neutrons with energies of 1 to 3 million electron volts are more biologically effective than those with greater energies. The results of the mass biological research done on the Manhattan Project are gradually being revealed and a great many more are soon to appear in the National Nuclear Energy Series. Some results of experiments done by Henshaw, Riley and Stapleton[7] in collaboration with Zirkle, Curtis and Cole at the Clinton and Metallurgical Laboratories of the University of Chicago have a direct bearing on the subject we are considering.

While studying acute lethal effects from single doses of gamma rays they found that when the radiation was given at the rate of 3 r per minute it required 1,200 r to kill 50 per cent of the mice whereas when it was given at the rate of 30 r per minute it required only 840 r. The same strain of mice was used in both experiments. In another experiment, they found that exposing mice over long periods to 51.6 r one day per week had more effect on reducing their life span than giving 8.6 r each day for six days per week (i.e. 51.6 r per week). They concluded that the distribution of ionization in "time" varies the biological effect in a way similar to the distribution of ionization in space.

They used several reactions to study the comparative effects of neutrons and roentgen rays. One of the most sensitive was a reduction of the life span of the mouse. Mice exposed to radiations might show no other detectable effect than a shortening of their life span. Using this as an indicator they found the relative biological effectiveness of pile neutrons to gamma rays to be 3.6 when single large doses were used and 14 when daily periodic small doses were used. This is the largest difference in effectiveness that they found and would seem to indicate that the cumulative effect of repeated doses of neutrons is much greater than that of repeated doses of roentgen rays. The range of doses used varied around 0.25 n of neutrons and 8.6 r of gamma rays per day.

In studying the effects on the peripheral blood, on the weight of the animals and on the repression of leukemia in a leukemic strain (C58) they found the relative biological effectiveness of the pile neutrons to gamma rays to vary around 3.4. Thus, they as others, found that neutrons are more effective than gamma rays for equal amounts of absorbed energy and that the ratio of effectiveness varied for each reaction studied.

FAST NEUTRON THERAPY

This brief survey of the vast biological field has shown how difficult it is to decide from animal experiments how to proceed to clinical experimental therapy. We started with the knowledge that for epilation of rabbits 1 n = 4 r and that for acute lethal effects on mice 1 n = 4 r and thought that if we used one-fourth as many n units as we were accustumed to use roentgens, we would be on safe ground. We soon found that for the threshold skin reaction on the human forearm 1 n = 6 to 7 r. Had we known then that for the chronic effect of shortening the life span 1 n = 35 r or that for some in vivo experiments with mice tumors 1 n = 50 r (Gray[5]) we might never have started.

From September 26, 1938, until June 20, 1939, we treated a total of 24 patients on the 37 inch cyclotron using 8 mev deuterons to produce the fast neutrons (Table

1). One of those patients is still alive. He had a carcinoma of the left upper lobe of the lung with metastases to the left supraclavicular region as proved by biopsy. He had roentgen therapy following the neutron therapy. He still has a hard mass in his neck but he has been healthy and active for the eight years since treatment.

In November, 1939, the cyclotron with 60 inch pole faces and giving deuterons with 16 mev of energy was ready for operation in the Crocker Radiation Laboratory. The apparatus and its operation were described by Aebersold.[1] The methods of treatment, early reactions and short term results were presented by Stone and Larkin.[13] The treatment of patients was continued until February, 1943, at which time Larkin entered the Naval Reserve, I had joined the Plutonium Project and the cyclotron itself was needed for the Manhattan Project. It is now more than seven years since treatments were started and more than four years since the last one was given. Sufficient time has elapsed to make it profitable to study survival periods and late effects.

TABLE I

FAST NEUTRON THERAPY

37 INCH CYCLOTRON OPERATING AT 8 MEV

Treatment Period September, 1938 to June, 1939

No. patients treated	24
No. patients surviving 8 years	1

60 INCH CYCLOTRON OPERATING AT 16 MEV

Treatment Period November, 1939 to February, 1943

No. patients treated	226
No. patients alive January 1, 1948	17
Surviving over 7 years	5
Surviving over 6 years	7
Surviving over 5 years	4
Surviving 4 yr., 11 mo.	1

In evaluating the results, several facts must be borne in mind. The patients selected for treatment with fast neutrons were, with one single exception, those considered incurable by any known means. Many of them had had previous treatment by means of surgery, roentgen rays or radium, or some combination of those methods. In some patients all of the known areas of involvement were not treated because the disease was too extensive; treatments were given to see what response would result in the area treated. The plan of treatment varied as experience was acquired. All of the treatments on the 60 inch cyclotron were given by the fractionation method and where possible by cross-fire techniques. The rate of administration varied around 5 n per minute. The cyclotron operated erratically, making it necessary to vary the rate of administration, the daily doses, the number of fields treated per day, the total doses and the number of days between the first and last treatments. Few if any patients received their treatments exactly according to the method planned. However, no treatment was considered complete unless a good erythema was produced and in the majority of cases some degree of epidermolysis was produced. Many radiologists consider that we overtreated rather than undertreated the patients.

The total number of patients treated on the 60 inch cyclotron was 226 (Table 1). One patient was treated on both cyclotrons and is included in both tables. For various reasons, both physical and mental, 31 of the patients did not complete their courses of treatments. A few had only one treatment but we have included every one who was accepted for treatment. On January 1, 1948, seventeen were alive, all but one, who lacked only one month, having lived more than five years from the day of his first treatment. Thus, 7.5 per cent of the total number survived five years or more. I believe that the average five year survival of an unselected group of patients whose cancers are not treated or not effectively treated is about 5 per cent. However, since the patients we treated were considered incurable and many had had other forms of treatment before coming to us, they would not be expected to survive as long as those in an unselected group.

PATIENTS NOW DEAD

The survival time of those patients who are now dead will be considered first. Table II shows the statistics according to the anatomical site of the lesions treated. The number of patients with lesions arising in any one area was not great. Patients with all kinds of malignant conditions were accepted in an attempt to give neutron therapy a wide trial. In general, the greatest shortest of those living through a complete series, one month and a half. Those patients with primary intrinsic lesions survived slightly longer than those with extrinsic ones, but the difference was very slight. As was reported before,[13] the persistence of necrotic ulcers of the larynx when the gross tumors disappeared was a serious complication. In 7 autopsy examinations, no tumor cells were found in the treated areas, but in

TABLE II

16 MEV NEUTRON THERAPY
Survival period of cases now dead
January 1, 1948

Location of Lesion	Total No. of Patients	No. Treated Completely	Average Survival	No. Treated Incompletely	Average Survival
Larynx	16	12	9 mo.	4	4 mo.
Pharynx	11	10	7 mo.	1	1 yr. 6 mo.
Tongue	18	15	7 mo.	3	4 mo.
Mouth	13	13	6 mo.		
Buccal mucosa	7	6	1 yr. 7 mo.	1	6 mo.
Lip	9	9	8 mo.		
Neck	20	19	9 mo.	1	1 yr. 11 mo.
Parotid gland	6	6	10 mo.		
Skin	8	7	1 yr.	1	10 mo.
Esophagus	8	7	4 mo.	1	2 mo.
Stomach	5	4	8 mo.	1	4 mo.
Colon and rectum	12	10	9 mo.	2	2 yr. 7 mo.
Anus	2	2	5 mo.		
Breast	11	9	1 yr. 4 mo.		
Prostate gland	24	24	2 yr. 8 mo.		
Brain	13	10	1 yr.	3	1 yr. 2 mo.
Lung	10	8	8 mo.	2	3 mo.
Miscellaneous	16	8	10 mo.	8	5 mo.

response to neutron therapy occurred in those lesions that ordinarily respond to roentgen therapy. Squamous cell carcinomas were affected considerably while adenocarcinomas of the stomach and intestines were altered very slightly if at all.

Larynx: There were 16 patients with malignant lesions of the larynx, 13 of whom had squamous cell carcinoma. Twelve patients had definite metastases and the others had such marked extension that one could not distinguish between the extension and metastases. The longest survival period was one year and seven months and the all there were ulcers showing no tendency to heal.

Pharynx: Included under pharynx are patients with lesions arising in the nasopharynx 7, in the hypopharynx 2, in the oropharynx 1, and in the tonsillar fossa 1. The persistence of non-healing painful ulcers was a factor in causing the short survival periods. The only patient surviving more than a year was a Chinese male who stopped coming in for treatment before the planned series was completed. He had a transitional cell carcinoma that ceased growing for a considerable period. Two

other patients with transition cell carcinomas survived for shorter periods than the average of the whole group.

Tongue and Mouth: None of the patients with primary lesions arising in the tongue and inside of the mouth lived very long in spite of some remarkable tumor regressions. As was to be expected, the patients with epidermoid carcinoma of the buccal mucosa survived longer than the others, some of them with apparent disappearance of the primary lesion and satisfactory healing. One patient lived nearly four years, one two and a half years and 1 one year and two months.

Neck: All patients treated for metastases in the neck only, the primary lesions having been controlled by other means of therapy, are grouped together. When reporting on the early results, we thought the response of metastatic lesions in the neck was very satisfactory. The relatively short survival time of this group clearly indicates that the initial response did not mean a cure.

Prostate Gland: The 24 patients with carcinoma of the prostate gland would appear, from the survival statistics, to have profited the most from their treatments. The introduction of hormone therapy and of orchiectomy in the management of many of these patients makes it difficult to evaluate the effect of neutron therapy on their survival. Of those dead, 5 lived more than four years and 6 others more than three years. The shortest survival time was nine months and the average for the 24 was two years and eight months. Twelve of them are known to have had metastatic lesions at the time of death. The damage of the normal tissues due to the radiation reactions was such that none of them lived comfortably. Six of them are known to have had persistent ulceration of one or more of the treated areas.

The miscellaneous group consists of patients with the following types of lesions: recurrent adenocarcinoma of the ovary 1; retroperitoneal metastases from a carcinoma of uterine cervix 1; abdominal metastases from a carcinoma of the testicle 1; retroperitoneal sarcoma 3; osteogenic sarcoma 2; sarcoma of chest wall 1; squamous cell carcinoma, metastatic in axilla 1; lymphosarcoma 1; myeloid leukemia 1; and Hodgkin's disease 1. None of them showed any unusual results as can be seen from the survival time.

Concerning the other groups of patients, little more can be said than is revealed by the statistics in Table II. Most of the squamous cell cancers of the lip, skin, esophagus and anus decreased in size and even

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Explanation of Color Plate

Fig. 1. Acute reaction, thirty-eight days after starting treatment. Treated through two opposing lateral fields three times a week, the total dose being 500 n to each field in forty-eight days. The black appearance of the crusts is due to the application of tannic acid.

Fig. 2. Chronic reaction, five years after treatment. Same patient as Figure 1. Note the blotchy atrophic skin, the absence of subcutaneous fat pad and the contraction of the scarred area.

Fig. 3. Chronic reaction, three years after a total dose of 673 n in twenty-four days. Note the blotchy atrophic skin. This patient has great difficulty in opening her mouth more than 1 inch.

Fig. 4. Chronic reaction, five years after a total dose of 500 n to each field in a period of twenty-nine days. The left buttock here shows ulceration. Later the center of the right scar broke down. Note the contraction of the tissues, telangiectatic vessels and atrophic skin. On palpation the tissues were hard down to and through the muscles.

Fig. 5. Chronic reaction, three years and four months after a total dose of 400 n to each field in fifteen days. Note the atrophic skin, telangiectasia and contraction of the central part of the fields causing a concave appearance that was not present earlier. Also, note the absence of subcutaneous fat.

Fig. 6. Chronic roentgen-ray reaction, seven and one-half years after treatment with 200 kv. roentgen rays, the total dose per field being 4,283 r (skin) in thirty-three days. Compare Figures 4 and 5. Note that the skin itself is atrophic and telangiectatic, but there is very little, if any, contraction and no depression because the subcutaneous fat has remained. On palpation the skin itself felt hard, but it was not bound down to the underlying muscles.

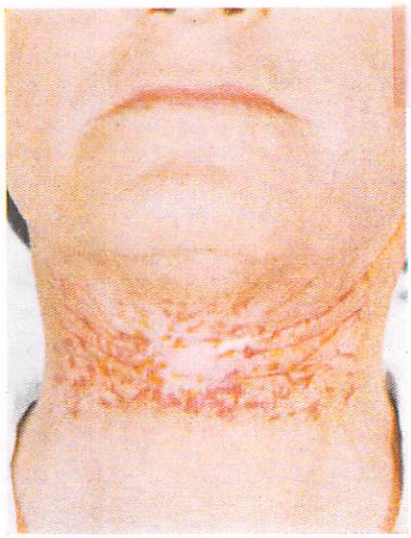

FIG. 2

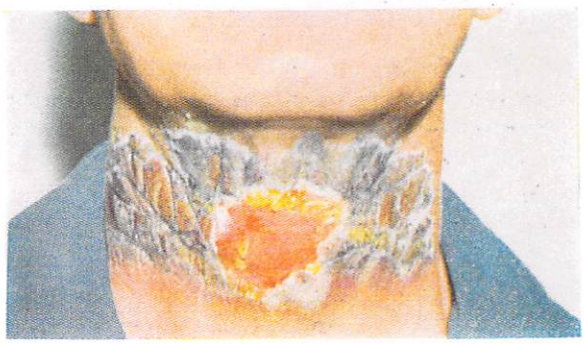

FIG. 1

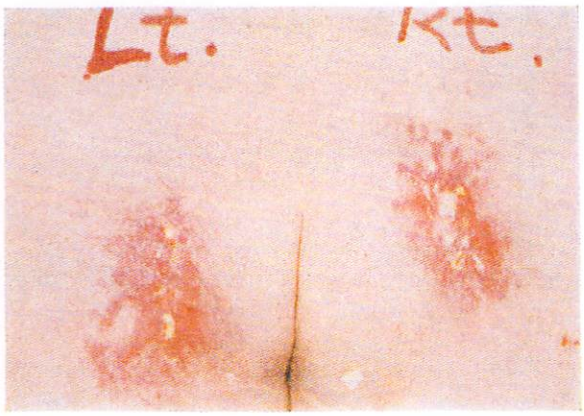

FIG. 4

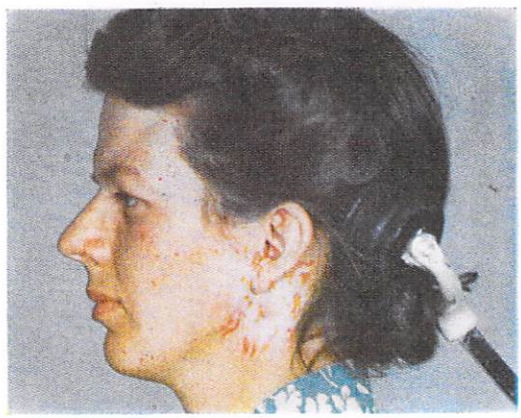

FIG. 3

FIG. 6

FIG. 5

the metastases in lymph nodes and bone seemed to be controlled when seen shortly after treatment. In some cases no cancer cells could be found by the pathologists in sections from the treated areas. In nearly all of the patients the damage to the normal tissues was great. The adenocarcinomas of the stomach, colon and rectum decreased somewhat in size following treatment but did not disappear.

The date of the death of all patients is known but unfortunately because the war caused the two principal investigators to leave and put a heavy load on those remaining, and because many of the patients did not live in or near San Francisco, autopsies were often omitted and the cause of death was often not established. The short survival periods, however, indicate that the patients were not cured. We know that many of the patients developed severe complications as a result of the treatments.

PATIENTS STILL LIVING

The present condition of those patients still alive should furnish the best information on which to judge the value of neutron therapy. In Table III the patients still alive on January 1, 1948, are grouped according to the location of the primary lesion and the average survival time is given. If patients are to be kept alive by any method of therapy, their condition several years after the treatments is a matter of great importance. Hence the histories of these patients will be given in greater detail.

Larynx: The patient with the laryngeal lesion was a salesman, aged fifty-eight, whose lesion was localized in the right vocal cord, with some fixation. He was the only patient treated with neutrons who might have been cured by roentgen rays, radium or surgery—the only exception to our rule. The biopsy diagnosis was squamous cell carcinoma. He had had no previous therapy and chose to be treated with neutrons. Starting on March 5, 1941, he was treated through two opposing lateral fields, each 7 by 7 cm. in size. Nineteen treatments were given in forty-eight days, with a total dose to each skin surface of 500 n. On the basis of 1 n = 6 r obtained from the threshold skin tests, he received a dose to each side equivalent to 3,000 r (skin) of roentgen rays generated by 200 kv. A weeping epidermolysis appeared on the thirty-third day and lasted fifty-two days. Figure 1 shows the condition on the thirty-eighth day after starting treatment. The only difference between his reaction and that frequently produced by us with roentgen rays is that it was most severe over the anterior surface of the neck. The skin healed well but before a year had passed it became very blotchy in appearance and the subcutaneous tissues became indurated. Gradually the skin became more atrophic. Telangiectatic vessels appeared after the third year. Figure 2 shows the appearance five years after treatment. He now has fixation of the skin and subcutaneous tissues to the larynx—the whole area feeling very hard and containing numerous telangiectatic vessels. There are somewhat similar changes on the inside of the larynx to those described for the outside. The lesion promptly disappeared and has not recurred. The patient is content because he has his voice and has lived without evidence of his cancer for more than six

TABLE III

16 MEV NEUTRON THERAPY
Survival Period of Patients Still Living
January 1, 1948

Location of Lesion	Number of Patients	Average Survival
Larynx	1	6 yr. 10 mo.
Lip	3	5 yr. 10 mo.
Neck, metastatic	1	6 yr. 7 mo.
Parotid gland	3	6 yr. 2 mo.
Skin, metastatic	1	7 yr.
*Anus, primary	1	6 yr. 11 mo.
Breast, metastatic	1	6 yr. 2 mo.
Prostate gland, primary	5	6 yr. 1 mo.
Shoulder	1	7 yr. 1 mo.

* Incompletely treated. Surgical cure.

years. We are not content because we believe that if roentgen rays had been used he might have been "cured" with less damage to the normal tissues.

Lip: Three patients each of whom had an epidermoid carcinoma of the lip have survived.

The first case was a man, aged fifty-seven, who came with a recurrent lesion of the center of the lower lip with extension to the mandible and floor of the mouth and with a small hard submental node. He had had four separate radium treatments and three surgical procedures. In October, 1940, he was treated with neutrons through one field 10 by 10 cm. in size centering on the chin and including the whole remaining lower lip. He was given fourteen nearly equal treatments in thirty-two days for a total of 1,025 n (=6,150 r ?). An epidermolytic reaction appeared on the thirty-eighth day and lasted 143 days. When it healed the epidermis was so thin that it appeared as a thin sheen over the red subcutaneous tissue. All evidence of cancer disappeared. During the second year after treatment the area below the lip ulcerated and the mandible started to slough. In the third year, the mandible, chin and all tissue from the treated area were removed surgically. The pathologists could find no cancer. The plastic surgeons are slowly rebuilding his face. It is now over seven years since his treatment. While his cancer was cured, he has had seven years of great discomfort. Radical surgery at the start would have been better.

The second of these 3 cases was a man, aged seventy-two, with an extension to the alveolar ridge from a previous epidermoid carcinoma of the center of the lower lip and large bilateral submaxillary masses. He had had roentgen therapy and two surgical procedures on his primary lesion. He was treated with neutrons at weekly intervals in January, 1943, through two opposing lateral fields each 7 by 7 cm. in size so that he received four treatments in twenty-two days to a total of 400 n to each side. Lysis appeared on the twenty-ninth day and lasted only seven days. When last seen he had atrophy and telangiectasis of the skin and fibrosis of the subcutaneous tissues. He also had a large submental fistula through which his tongue protruded and his mandible was sloughing. There was no gross cancer present. After five years and an equivalence of only 2,400 r (6×400 r) this man has very severe skin changes.*

The third case of this series had a large left submandibular mass that recurred after surgery. The primary epidermoid cancer of the lip had been "cured" by roentgen therapy. In January, 1943, he was treated with neutrons through one field 10 by 5 cm. in size directly over the mass. Three treatments were given in fifteen days at weekly intervals, 200, 200, and 100 n, to a total of 500 n. Epidermolysis was present on the twenty-third day and lasted over thirty days. The tumor disappeared slowly. The skin healed but in a year ulcerated. It healed again while being treated with radon ointment. Now, nearly five years later, he has no evidence of tumor, but the skin is atrophic, with telangiectasia, and the subcutaneous tissues are very hard. If 500 n=3,000 r so far as the acute reaction is concerned it is equal to many more in so far as the late reaction is concerned.

Neck: A female patient, aged fifty-four, had a biopsy from a mass 4 by 4 cm. in size on the left side of her neck. The pathologist's diagnosis was metastatic squamous cell carcinoma. No primary lesion was located. In June, 1941, she was given ten treatments with neutrons in twenty-two days to a total of 670 n through a portal 7 by 7 cm. in size. Epidermolysis appeared on the forty-third day and lasted eighteen days. Now she has thin dry atrophic skin with no subcutaneous fat, but with fibrosis. She has no evidence of cancer. She had some ulcerated teeth removed from just above the treated area, with no complications.

Parotid: Three patients who had parotid tumors have survived seven years eight

* Since writing this lecture I have received word of the death of this patient.

months, six years three months, and five years respectively. The first and third had mixed cell tumors and still have small masses that are not enlarging. The second one had a carcinoma recurrent after surgery and now has no evidence of it. All were treated through single portals directly over the parotid, the first patient receiving a total exposure of 425 n in ten treatments in thirty-five days; the second receiving 673 n in eleven treatments in twenty-four days; and the third 600 n in three treatments in fifteen days. The treatments to the first patient produced a dry desquamation only, those to the other 2, epidermolytic reactions lasting sixteen days and eleven days. All now have trouble with jaw movements. All have skin atrophy, absence of subcutaneous fat and subcutaneous induration (Fig. 3). The one receiving the largest dose developed an ulcer during the third post-treatment year which healed while being treated with radon ointment. The one receiving the smallest dose developed radiation osteitis and a draining sinus during the sixth post-treatment year. Thus, a dose of even 425 n given in 7×50 n plus 3×25 n fractions in an elapsed period of thirty-five days to a colored boy of nineteen years, resulted in too severe late changes in the skin of a usually resistant area.

Skin: The patient listed under "skin" was a man, aged sixty-nine, who had had a primary epidermoid carcinoma on the upper half of his left ear. The surgeons had removed the upper half of his ear. He came to us in December, 1940, with a hard mass 5 cm. in diameter and at least 1 cm. thick, under the skin and fixed to the deep structures immediately anterior to the area of excision. He was given four treatments of 75 n each and three of 100 n in eight days, a total of 600 n to a field 10 by 10 cm. in size. Epidermolysis began on the twenty-first day and lasted sixteen days. By the end of one year the skin was blotchy and telangiectatic vessels were appearing. Since then the skin has become very atrophic; the subcutaneous fat layer has disappeared; and all the tissues from the skin to the skull have become very hard. During the fifth year an ulcer appeared in the treated area but healed. The tumor disappeared before the acute reaction subsided and has not recurred. Both the immediate and late reactions to 600 n given in eight days were greater than I would expect from 3,600 r of roentgen rays generated by 200 kv. and given in the same way.

Anus: The patient with the squamous cell carcinoma of the anus was a woman fifty-five years of age who came for therapy in January, 1941. She had had previous treatment with roentgen rays and radium but the cancer was regrowing. After receiving five treatments of 50 n each in ten days she refused further irradiation and one month later submitted to an abdominoperineal resection. Some carcinomatous cells were found by the pathologist, but he said they were degenerating. She now has slight skin atrophy and telangiectasia, but since she had had roentgen and radium treatments one cannot say that the changes are due to 250 n of neutron radiations.

Breast: The patient listed under "breast" came to us with a hard nodule in the supraclavicular area. She had had a radical amputation of her breast for a comedo carcinoma, followed by a full course of irradiation by roentgen rays to the chest wall, axilla and supraclavicular area. In April, 1941, she was given ten treatments of 50 n each in twenty-seven days to a single field 10 by 10 cm. in size. The supraclavicular area is now so hard that it is impossible to tell whether any tumor remains. The skin is atrophied. The combination of treatments caused the late changes—but the nodule that appeared after the roentgen therapy disappeared after the neutron therapy.

Prostate Gland: Five patients who had carcinoma of the prostate gland were still alive on January 1, 1948. When treatments were started, 1 was forty-nine, 2 were sixty-one, 1 was sixty-three and 1 was seventy years of age. Four had had transurethral resections and one an enucleation of the

prostate. No metastases were known to exist but there was local extension beyond the gland in all of them. One has lived more than seven years, 2 more than six years and 2 more than five years. Two are known to have metastases. Three are known to have marked induration in the region of the prostate, but this condition has not altered for several years so far as can be told by palpation. Three have had orchiectomy and are taking diethyl stilbestrol. Two have had neither orchiectomy nor hormone therapy and are apparently free of metastases.

All were treated through three portals, one anterior through the pubic region 10 by 10 cm. in size, two posterior, through each gluteal region 10 by 15 cm. in size. Three were exposed to approximately 500 n to each field, 1 receiving sixteen treatments in forty-five days, 1 eleven treatments in twenty-nine days and 1 ten treatments in twenty-five days. All of these patients developed an epidermolytic reaction in all fields, the main difference being that it appeared sooner in the patient treated in the shortest time. The other 2 patients had three treatments each in fifteen days (weekly intervals), each field being exposed to a total of 400 n. These treatments resulted in erythematous reactions with no lysis except a slight amount in one anterior field. In spite of the different methods and the different primary reactions all 5 cases developed late changes which were detectable before one year had elapsed. The skin became blotchy, white, telangiectatic and adherent to the underlying tissues. The subcutaneous fat disappeared. The skin, subcutaneous tissues and underlying muscles in all areas became united in hard masses which shrunk as time passed and distorted the structures in and near the treated areas. The gluteal induration made sitting painful and walking difficult. The indurated pubic areas blocked lymphatics with a resultant edema of the penis and scrotum. The contraction of the tissues in the anterior fields resulted in distortion of the penis, since its base was involved. One of the patients who was exposed to 500 n per field developed an ulcer anteriorly during the second year and a necrotic ulcer in the left gluteal field during the fifth year. Each of these ulcers took several months to heal. Still later, the skin in the right gluteal area broke down and the resulting necrotic ulcer has persisted for about one year. Another patient who was exposed to 400 n developed an ulcer in the anterior field. At least 5 of the patients who are dead had developed very severe painful ulcers in fields treated with no greater doses than those reported above. Some of the changes are shown in Figures 4 and 5, but unfortunately illustrations do not show the induration.

Shoulder: The last patient to be reported is a woman who had a fibrosarcoma on her left shoulder that had regrown in the scar of a second surgical excision. When she came to us in November, 1940, the tumor was 3.5 cm. in diameter and 2 cm. thick. She was given fifteen treatments in thirty-four days to a single field 10 by 10 cm. in size, the total dose being 1,075 n. A severe epidermolytic reaction appeared on the fifty-seventh day and from that time on the skin never healed. The resultant painful ulcer progressed in spite of all types of treatment and eventually pieces of the scapula sloughed from the bottom of the lesion. Two years passed with no evidence of metastases. It was decided to remove the necrotic area by a shoulder girdle amputation. The pathologist found no evidence of tumor in the removed tissue.

DISCUSSION

Sixteen patients who received complete courses of treatment with fractionated doses of fast neutrons have been observed for more than five years. Thirteen of them had severe epidermolytic reactions in all the treated areas; 1 had epidermolysis in one of three fields; 1 had an erythematous reaction; and 1 had only desquamation. Three patients had epidermolysis in gluteal fields, 1 in a field over the shoulder and 1 in a supraclavicular field. Most of them there-

fore had severe early reactions and late changes were to be expected. Even when this fact is taken into consideration, the late changes are more marked than were expected.

To compare the reactions produced by fast neutrons with those produced by roentgen rays, similar regions must be selected. This limits the present study to very small groups or individual patients and patients vary greatly in their reaction to roentgen rays even when treated by identical techniques. In spite of this, some comparison seems desirable.

The patient who had carcinoma of the larynx received a total exposure of 500 n to each of two opposing fields in forty-eight days. To produce an acute reaction similar to his (Fig. 1) would require a total exposure of considerably more than 3,000 r (skin) of filtered roentgen rays generated by 200 kv. when given in a similar time. If this is true, then 500 n = >3,000 r or 1 n >6 r. If 4,000 r was the required exposure then 1 n would equal 8 r. The late changes in the patient treated with neutrons were very marked (Fig. 2). We have produced as severe early reactions in patients treated with roentgen rays, and at the end of five years they have shown only a little skin atrophy and no fibrosis. From these considerations it is apparent that because the r/n ratio is 6/1 for a threshold skin reaction it will not necessarily be the same for the epidermolytic reaction or for the late atrophy and fibrosis reaction. The relative biological effectiveness of the two radiations varies for each reaction even when they occur in the same tissue.

The reactions seen in the gluteal region emphasize the above conclusions. Very marked skin atrophy, loss of subcutaneous fat and fibrosis of muscles resulted from a total exposure of 400 n in fifteen days as shown in Figure 5. The acute reaction in this field had been a first degree erythema. The appearance of the right gluteal area of a woman who had been treated seven years earlier with a total exposure in thirty-two days of 4,283 r (skin) of roentgen rays generated by 200 kv. is shown in Figure 6. While her skin is atrophic, blotchy and telangiectatic, some subcutaneous fat remains, fibrosis is less marked and no contraction of the area has occurred. Admitting the inaccuracy of comparing single individuals of different sexes it might be said that 400 n produced much more marked late changes than 4,000 r, or the r/n ratio is greater than 10.

This report has been limited largely to a discussion of the survival periods and skin reactions; however, the reactions of the deeper tissues have also been severe. Persistent ulceration in the site of tumor regression in those patients who had lesions of the mouth, pharynx and larynx has already been mentioned. The regenerative ability of the normal tissues apparently was damaged by a dose of neutrons which was not great enough to kill all cancer cells in all patients. Some of the patients treated through the mandible developed radiation osteitis. When the treatments were given through the pelvis, the effects on the intestine were quite severe. One patient who has lived more than five years has had very little bowel control for the last two years. By digital examination and by roentgenographic means the rectum and lower portion of the sigmoid were found to be relatively rigid, with little power of contraction. These few examples of the types of internal damage indicate that the patients were thoroughly irradiated in the depths.

While survival is important, the condition of patients surviving is of equal importance. Eighteen of 249 patients treated by fast neutrons on both cyclotrons have lived from almost five years to more than eight years since starting their treatments. Eight are apparently free of cancer. Eight others have so much induration in the region of the original tumor that it is not possible to decide whether or not any cancer is still present in the primary site, but 2 of them have metatastes. The remaining 2 have persistent small masses. Three of the 8 cases who are free of cancer had the treated areas removed by surgery,

2 having no cancer cells and 1 having "degenerating" cancer cells in the removed tissue. While all 18 have severe late reactions, 12 of them have such severe changes that they are partially incapacitated. These results are not encouraging even though some patients have been kept alive.

SUMMARY AND CONCLUSION

1. The physical measurement of neutron radiations in air in units that can be translated to tissue doses comparable to tissue roentgens has been difficult. The n unit of exposure is physically equivalent to about 2.5 roentgens as judged by the amount of energy absorbed from a beam by tissue. In other words, 1 n = 2.5 rep (roentgen equivalent physical).

2. Gross and microscopic studies of mammalian tissues have shown little or no qualitative difference in the reactions produced by neutron and roentgen-ray radiations.

3. The relative biological effectiveness of various radiations, as judged by the amount of energy absorbed from the beam in producing a given reaction, varied greatly from one test object to another and from one reaction to another even in the same tissue.

4. In general, the relative biological effectiveness of radiations on mammalian tissue was greater the higher the specific ionization. Neutrons were more effective than roentgen rays per unit of energy absorbed by tissue. It was hoped, therefore, that they might be more effective in the treatment of human cancer.

5. Biological work on the Plutonium Project, and the human work here reported, shows that the relative biological effectiveness of neutrous compared to roentgen rays is greater for late than it is for early effects. Whereas, 1 rep of neutrons might equal 2.5 r of roentgen rays for a threshold skin reaction, it might equal 4 r for late skin effects and even 15 r for the chronic effect of shortening the life span by repeated daily doses.

6. Biological work showed that for some effects of radiations, the distribution of ion pairs "in time" played a part similar to that of the distribution in space. The rate of administration was not sufficiently weighted in the treatment of patients.

7. From a study of the patients treated with neutrons it is clear that cancer cells can be killed and patients "cured" of their cancer, but the difference between the dose required to kill cancer and that to acutely damage normal tissue is very small. The difference is even less when reactions occurring several years after treatment are taken into account.

8. Eighteen patients have been kept alive, but none of them are free from distressing late effects.

9. Anyone contemplating the use on patients of new radiations such as multimillion volt protons, beta rays and roentgen rays should study the relative biological effectiveness of them by late reactions as well as by acute early ones.

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